

Vaccinations for Adult Solid-Organ Transplant Recipients: Current Recommendations and Protocols

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INTRODUCTION

Outcome and survival after solid-organ transplantation improved significantly in the last 15 years, leading to a need for new and effective preventive measures to maintain general health (104). Immunosuppressive regimens put these patients at higher risk of life-threatening infections. Vaccinations can prevent disease and decrease the replication and dissemination of infectious microorganisms. Therefore, specific vaccines have been recommended, including pneumococcal, influenza, and hepatitis A and B. Also indicated, in selected cases, are tetanus, diphtheria, and *Haemophilus influenzae* type b.

However, the efficacy, safety, and protocols of several vaccines in this patient population are poorly understood. Due to immunosuppression regimens, several questions arise. First, what is the effect of immunosuppression on the durability of pretransplant vaccinations, given both early and in end-stage organ disease? Second, are vaccinations effective when administered after transplantation, in both the early and late periods? Third, what are the side effects of live and inactivated vaccines in immunosuppressed patients and what is their impact on graft function?

In this review we discuss the general and specific issues related to vaccination in adult solid-organ recipients that are pertinent to these questions. We also outline protocols for

specific vaccines including timing, doses, and administration that are peculiar to this patient population.

GENERAL PRINCIPLES

It is usually accepted that, in solid-organ recipients receiving immunosuppression, the immune system will not be able to mount a response as effective as in normal subjects (5). Most immunosuppressive regimens after solid-organ transplant include a combination of steroids and calcineurin inhibitors, such as cyclosporin and tacrolimus (FK506). Under these regimens, both T- and B-cell responses are impaired through blockage of cellular proliferation after antigen stimulation as well as inhibition of cytokine production necessary for such stimulation (95). Corticosteroids are potent cytokine inhibitors (interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor, and gamma interferon) and block antigen-induced T-cell proliferation. However, immunosuppression with steroids alone does not seem to completely impair the immune response to vaccine administration (68). Calcineurin inhibitors directly inhibit interleukin-2-dependent T-cell proliferation and, blocking interleukin-4 and interleukin-5 production by T cells has an inhibitory effect on B-cell function and antibody production. Azathioprine and mycophenolate mofetil, also used as third-line agents, interfere with purine synthesis, although at different steps, blocking both T- and B-cell proliferation (95). The combination of these mechanisms leads to significant impairment of the entire immunologic cascade following antigen presentation to immune cells. Whether the use of specific agents and the total amount of immunosuppression received is im-

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portant in causing an impaired response to vaccine is not known.

Other specific mechanisms also need to be considered. Of particular importance appears to be the presence of posttransplantation hypogammaglobulinemia. This phenomenon, described in heart, kidney, and lung recipients, has been associated with the development of recurrent infections (42, 84, 102). In the study by Goldfarb et al., patients with hypogammaglobulinemia (immunoglobulin G < 600 mg/dl) lacked protective response to pneumococcus in 30%, diphtheria in 15%, and tetanus in 19%. Patients with immunoglobulin G levels of <400 mg/dl had poorer survival and were at high risk of tissue-invasive cytomegalovirus infection (42). Waning natural immunity and impaired de novo antibody response may cause impaired seroprotection after solid-organ transplantation the same way that has been described in bone marrow recipients during the late posttransplantation period (5).

The production of new memory cells as well as the survival of memory cells acquired prior to transplantation is critical to an effective response to vaccines. The effect of immunosuppression on immune memory cells is not completely understood and the specific life span of memory T cells have not been determined in these patients. There is evidence, however, that recollection of pretransplant immune memory, with one or more booster doses of a vaccine, may be more effective than primary vaccination (14). The cellular mechanisms leading to an impaired production of memory cells during immunosuppression should be further evaluated.

STRATEGIES TO IMPROVE RESPONSE

Timing of Immunization

Timing of vaccination appears to be critical to optimize response. Data regarding timing of vaccination are scarce in the adult literature, and we need to extrapolate results from pediatric studies. As a general rule, the primary immunizations should be given before transplantation, as early as possible during the course of disease since the immune response to vaccines is decreased in patients with end-stage organ disease (11) (Table 1). The first 6 months after transplantation are associated with the poorest response because the patients are usually receiving the highest doses of immunosuppression (89). This period has also been associated with a higher chance of graft dysfunction and rejection. For example, caution has been recommended for tetanus vaccination series in the first 6 months after transplantation in children (20). Administration of immunizations too close to transplantation may also result in ineffective protection (80). An initial reduction in antibody titers immediately after vaccination has been described in children (26). A strategy of early measles-rubella vaccination in infants with chronic renal failure was effective in inducing immunity in most patients and may allow transplantation by achieving immunity earlier than traditional vaccination schedules (36).

Immunoadjuvants

Little is known on the role of immunoadjuvants in patients after solid-organ transplant. Although their use has been rec-

TABLE 1. Vaccinations in patients after solid organ transplantation.

Type of vaccine	Current recommendation
Pneumococcal	Before and after transplantation
Influenza	In patients and household members before and after transplantation
Tetanus	Before and after transplantation
Diphtheria	Before and after transplantation
Haemophilus	Before and after transplantation
Hepatitis A ^a	For travelers to endemic areas before and after transplantation
Hepatitis B ^b	Before and after transplantation
Rubella	Controversial
Varicella	Controversial
Oral Polio Vaccine ^c	Contraindicated in patients and household members
Vaccinia	Contraindicated in patients, household members and health care workers in transplant centers
Yellow fever	Contraindicated
BCG ^d	Contraindicated

^a The vaccine is recommended in all liver transplant recipients.

^b Can be decided on a patient base in heart and lung recipients.

^c The recommended polio vaccine for transplant recipients is the inactivated polio vaccine.

^d BCG, bacillus Calmette-Guerin.

ommended in immunocompromised hosts (51), the available literature is scarce. Hepatitis B vaccine has been studied more extensively. Interferon and interleukin-2 were used in the 1980s as adjuvants in low responders to hepatitis B vaccine (44, 78). Interleukin-2, in particular, was used in patients with uremia with 70% seroconversion without major side effects. More recently, granulocyte-macrophage colony-stimulating factor was used in the same patient population with controversial results (6, 47, 59).

Other adjuvants include aluminum compounds, the hormone dihydroepiandrosterone sulfate and several cytokines (82). More recently the compound MF59 has been used together with hepatitis B virus vaccine in normal adults with promising results (48). For these compounds there are no data available in immunocompromised patients in general. Furthermore, their safety in patients after solid-organ transplant needs to be established and the risk of rejection directly caused by immunoadjuvants should be excluded.

Monitoring Immune Protection

While monitoring protective titers in immunocompetent hosts is usually not necessary, in organ transplant recipients it may be useful. Patients who are not protected should receive additional trials of immunization until the protective titer is reached. However, assays to assess optimal response after immunizations are not always available and standardized (40). These assays may not convey whether the patient will necessarily be protected from infection with a given pathogen because, in some instances, achievement of a protective titer does not always correlate with true protection from infection. For these reasons one should remain vigilant.

Nevertheless, titers can be measured after vaccinations. Protective antibody titers to most common vaccinations are summarized in Table 2. Established recommendations include monitoring of postvaccination titers for hepatitis A and B but

TABLE 2. Proposed protocols for vaccinations in solid-organ transplant recipients

Vaccine	Preparation	Dose	Frequency
Hepatitis A	Inactivated	1,440 ELISA units	0 and 2 mo
Hepatitis B	Recombinant	40 µg	0, 1, 2, and 6 months
Influenza	Trivalent inactivated	Double dose	Annually, in October-November
Pneumovax	23-valent polysaccharide, heptavalent protein conjugated	Routine	Every 2-5 years
Tetanus	Toxoid	Routine	Booster every 5 years
Diphtheria	Toxoid	Routine	Booster no later than 2 years from vaccination and then every 10 years

not for influenza (20). Titers after vaccination for hepatitis B are commonly done also in immunocompetent adults. Monitoring of total immunoglobulin levels (total immunoglobulin G, A, and M) may allow recognition of those patients who are at higher risk of not responding to vaccination and of being unprotected from prior vaccines. Although we think that monitoring of immunoglobulin levels during immunosuppression could be useful in predicting response to vaccinations in selected patients, more studies are needed to clinically validate this approach. We recommend monitoring specific postvaccination titers for hepatitis A and B viruses and influenza virus only on a case-to-case base.

Vaccination of Health Care Personnel and Household Contacts

Vaccination of household contacts and health care workers of transplant centers is recommended. Household contacts may receive almost all vaccinations with minimal risks to patients (20). Exceptions are oral polio vaccine, vaccinia, and, according to some, varicella. Varicella vaccine is recommended in unprotected health care workers in general (46). This can reduce the risk of contracting the disease, which can be severe in adults, and decrease the rate of nosocomial varicella-zoster virus transmission (46). We recommend applying this rule to all personnel working in transplant centers and seronegative household contacts of patients. Avoidance of contact with transplant recipients after vaccination for those healthcare workers who develop a rash has been recommended (46). However, since the risk of transmission of a vaccine strain to a patient is very small, there is no agreement on this issue among different experts.

Influenza vaccine is strongly recommended annually for all health care workers and household contacts (32). This may be life-saving for patients, preventing their exposure to the virus during an epidemic.

SAFETY OF DIFFERENT VACCINES

Risk of Rejection

Theoretical concerns have been raised regarding the potential for triggering rejection with vaccinations. An enhanced lymphocyte proliferative response to donor-specific aortic endothelial cells following influenza vaccination has been reported (100). The data available in the literature, however, do not support this concept (43). Influenza vaccine has been initially reported to cause low level rejection in heart recipients by some (15), but others did not confirm this finding (66). Recent

studies showed that influenza vaccination, in the same patient population, does not promote cellular and humoral activation causing graft rejection and allosensitization (64). We are not aware of any reported case of rejection triggered by influenza vaccination in liver, kidney, and lung recipients. Tetanus toxoid was also reported to trigger rejection in anecdotal reports that have not been confirmed (52). Furthermore, several viral infections have been reported to trigger rejection (1, 17, 32, 59). A rejection epidemic among renal recipients was described in association with influenza A Victoria in 1978 (61). Influenza B and adenovirus infections were also associated with rejection in these patients (39). These data suggest that the infectious agent, more than the vaccine, is a cause of rejection, and effective immunizations may actually be protective.

Live Vaccines

The safety of live attenuated vaccines in adult recipients is poorly known. Few studies have been performed in those pediatric recipients that are unable to complete their vaccination cycles because of transplantation. Some vaccines are absolutely contraindicated in solid-organ transplant recipients. These include oral polio vaccine, vaccinia, bacillus Calmette-Guerin, and live oral typhoid (11). Although yellow fever vaccination has been used in case reports with human immunodeficiency virus infection (86), no data are available in solid-organ recipients. In our opinion the vaccine should be considered contraindicated. Oral polio vaccine is contraindicated also in family members of transplant recipients because of possible contagion by shedding of the virus and close contact with excreta. Inactivated polio vaccine is safe and effective in renal transplant recipients (55). For safety concerns, the killed parenteral Vi polysaccharide vaccine for typhoid fever should be used instead of the live attenuated oral Ty21a (82). No data on the efficacy of this vaccine in organ transplant recipients are available.

Varicella can cause a severe infection in immunosuppressed individuals, and vaccination is recommended prior to transplantation in children and adolescents (17) as a cost-effective measure to reduce morbidity and costs (65). Broyer et al. demonstrated that pretransplant vaccination in 704 pediatric renal transplant recipients between 1973 and 1994 was effective in reducing the incidence of disease from 45% in nonvaccinated patients to 12% in those who were vaccinated with no deaths related to varicella-zoster virus in the vaccinated group (17). Vaccination for varicella has also been recommended for seronegative household contacts of immunocompromised patients by the American Academy of Pediatrics. Only 5 to 10%

of adult patients in the United States are seronegative for the virus, with higher percentages in tropical countries (46).

The available vaccine is a live attenuated strain of varicella virus named the Oka strain (67). Varicella vaccine was given to 17 pediatric renal patients and resulted in one case of mild varicella at 2 weeks and three additional cases after 2 to 4 years. Antibody response was 76%, but response was delayed (103). Concerns about the use of the vaccine in immunosuppressed patients have been raised and include the possibility of reactivation of the Oka strain (67), transmission of vaccine virus to the general population and development of zoster (46). However, the rate of zoster after vaccination was lower than after natural infection in a population of children with leukemia (18). In a different study, the incidence of zoster was 7% in pediatric renal recipients who received the vaccine, compared to 38% of those who developed primary infection after transplant (17). Use of varicella vaccine remains controversial in adult solid-organ recipients and the efficacy in this patient population is unknown suggesting the need for long-term large studies that provide additional data on outcomes.

Measles-rubella is also a live attenuated vaccine, but its use in adults is rarely required. The exception to this is prevention of rubella in young female patients. Rubella infection does not cause severe infection in solid-organ recipients, but the congenital rubella syndrome is a concern because of the increased number of pregnancies in young women of child-bearing age who survived transplantation. Since the vaccine was proven to be safe and effective in bone marrow recipients (73) and patients with human immunodeficiency virus (38), some authors recommend vaccination of all seronegative female transplant recipients before pregnancy (20). However, after bone marrow transplant, measles-rubella revaccination is recommended after at least 2 years posttransplant in those patients who are stable and without graft-versus host disease (21). A small study of measles vaccination in pediatric liver recipients showed that immunity developed in 7 out of 18 vaccinated children (85). No complications directly attributable to the vaccine were reported. Since no large clinical trials of safety and efficacy in adult solid-organ recipients are available, we recommend caution.

SPECIFIC RECOMMENDED VACCINATIONS

Pneumococcal Vaccine

Solid-organ transplant recipients may develop severe infection with *Streptococcus pneumoniae* (4). Vaccination has been recommended in heart, renal and liver recipients. Available vaccines are the 23-valent polysaccharide and the heptavalent protein conjugate. The latter has been reported to be more immunogenic in pediatric patients but does not cover all serotypes (57). No studies on the use of the heptavalent vaccine in adult transplant recipients are available.

Patients with end-stage liver disease and liver transplant recipients are at risk from *Streptococcus pneumoniae* peritonitis, pneumonia and sepsis. Early studies in patients with cirrhosis showed good response to the pneumococcal vaccine. Patients with alcoholic cirrhosis produced adequate titers at 3 months with a 14-valent polysaccharide vaccine (83). Increased antibody and opsonic titers were demonstrated in both serum

and ascitic fluids (92). More recently McCashland et al. found immunoglobulin G production to the 23-valent pneumococcal vaccine to be decreased in cirrhotics compared to controls. Furthermore, cirrhotic patients had a more rapid decline in IgA and IgM titers at 6 months. When followed during liver transplantation, immunoglobulin G and A levels dropped below baseline levels 3 months after transplantation (77).

This loss of protective titers is not unique to liver recipients and has been described in renal (72) and heart recipients (4). Heart recipients were found to have a suppressed response to the vaccine compared to controls (14). However, in those patients who have been vaccinated and in whom pneumococcal vaccine was repeated, there was a higher response compared to those who were vaccinated for the first time (14). Others found a good response to pneumococcal vaccine in heart recipients comparable to controls (27). In the same study, the immune response to influenza vaccine administered at the same time was significantly impaired, suggesting that the polysaccharide antigens of the pneumococcal vaccine might stimulate a stronger T-cell-independent antibody production.

The immunogenicity of the polyvalent pneumococcal vaccine was decreased in patients on chronic dialysis compared to controls (89). On the other hand, patients on dialysis had greater pre- and postvaccination titers than renal recipients, although both groups reached protective antibody titers after vaccination (72). However, this protection appears to be only short-term in renal recipients (60), and functional opsonic antibodies were significantly lower in these patients compared to controls (10).

Taken together, these results suggest that solid-organ recipients can respond to pneumococcal vaccine with a significant rise in titers compared to the prevaccination period (28, 77). However, their immune response is less intense and of shorter duration than in normal controls. Primary immunization should be started before transplantation (71) and repeated booster doses should be administered at 2 to 5 years intervals (12, 52). New approaches with combined 23-valent and heptavalent protein conjugated vaccines deserve clinical attention.

Influenza Vaccine

Influenza infection has higher morbidity and mortality in patients after solid-organ transplantation (3), and has been associated in rare occasions with development of graft rejection (32). Efficacy of vaccination for influenza in immunodepressed individuals is controversial. The composition of the influenza vaccine changes yearly, and variations in the immunogenicity of the vaccine strains used must be considered when analyzing results from prior trials.

Immune response in renal and heart transplant recipients has been described both adequate and impaired (2, 9, 13, 16, 98). Fraund et al. vaccinated 79 heart recipients with the 1996/1997 trivalent vaccine. The vaccination was well tolerated and effective but the antibody levels were lower than healthy controls (37). Pediatric patients after both renal and liver transplantation were protected by influenza vaccination (76), although the percentage of pediatric liver recipients with protective antibody titer 1 month after the vaccination was only 67% in one study (75).

Data in adult liver transplant recipients are also controver-

sial (31, 75, 77). We recently found that liver recipients had an impaired immune response to the A/Sidney/H3N3 antigen of the 1999 to 2000 trivalent vaccine compared to controls (31). Soesman et al., in a larger study from the Netherlands, also described a decreased immune response in adult recipients, when compared to both cirrhotics and controls. They also demonstrated an increased efficacy of a double dose of influenza vaccine as well as a correlation between seroconversion and a specific *in vitro* T-cell response against influenza virus (93). On the other hand, a recent study from Germany found good antibody response in liver recipients, which was comparable to controls (19).

These data suggest that the postvaccination antibody titers to influenza, in solid-organ transplant recipients, are lower than healthy controls. Although these patients, as a group, show a significant increase in titer after vaccination, individual patients may remain unprotected from influenza infection. Severe complications of influenza leading to death have recently been described in a liver recipient despite routine vaccination (98). Since side effects and risks of the vaccination are minimal, we strongly recommend vaccination in patients, household contacts, and all personnel of transplant centers (32). Additional booster doses in patients with nonprotective titers should be considered. No data are available on new preparations of influenza vaccine.

Hepatitis A

Infection with hepatitis A virus in patients with cirrhosis awaiting transplantation may cause severe disease and death (70) (25) (62). Vaccination is recommended as soon as possible in the course of liver disease for those patients that are not immune to hepatitis A. Vaccination is also recommended in other solid-organ recipients traveling to areas endemic for the disease. Hepatitis A vaccine induced >95% seroconversion in patients with compensated liver disease (63), although the immune response appears to be less intense than healthy volunteers (69). Development of liver failure is associated with a decreased response to the vaccine (33).

After solid-organ transplantation, response is also poor. In a recent study, none of eight liver transplant recipients responded to the hepatitis A vaccine (33). Seroconversion in renal recipients was 24% after the first dose of the vaccine and 72% after the second. However, the geometric mean titer of anti-hepatitis A virus was lower in renal recipients compared to controls and liver recipients (94).

After transplantation there is also loss of protective antibody titers to hepatitis A (7). At 2 years from transplant, 41% of liver and 74% of renal recipients who were successfully immunized had antibody titers below the protective level (45). Some concerns have been raised on the cost-effectiveness of hepatitis A vaccine in patients with chronic hepatitis C (79).

Hepatitis B

The need for vaccination against hepatitis B comes from the observation that all solid-organ recipients may have a more rapid and severe progression of hepatitis B as well as reactivation of latent infection due to immunosuppression (52). Furthermore, effective protection against hepatitis B may increase

the safety of a transplant of a nonhepatic graft from a donor who is hepatitis B surface antigen negative and core antibody positive. Vaccination for hepatitis B has been specifically recommended before liver transplantation to prevent *de novo* graft infection (35) and in renal transplant recipients because of the increased risk of exposure. Recombinant vaccine containing hepatitis B virus surface antigen has been available since 1989 (82).

In patients awaiting liver transplantation, the severity of liver disease is inversely correlated with the efficacy of hepatitis B vaccine. The immune response to the standard dose in patients with advanced cirrhosis awaiting liver transplantation leads to seroconversion in only 16% to 28% of patients (22) (99). Patients with longstanding chronic hepatitis C have an increased rate of primary nonresponse to the vaccine compared to controls (31 versus 9%) (101).

In order to overcome these difficulties, different protocols of hepatitis B vaccination have been proposed, including accelerated schedule, increased doses and repeated vaccinations (30, 58, 88). An accelerated schedule with injections of 20 µg of recombinant hepatitis B virus surface antigen at 0, 7, and 21 days has been studied in 20 liver transplant candidates with child B (*n* = 7) and C (*n* = 13). While immunocompetent controls reached 100% seroprotection (anti-hepatitis B virus surface antibody > 10 mU/ml) at 8 weeks after the booster dose, cirrhotics had only a 36% incidence of seroprotection (58).

Increasing the vaccine dose leads to better results. Rosman et al. used 40-µg doses of recombinant hepatitis B vaccine at 0, 1, 2, and 6 months and compared this protocol to the standard 20 µg at 0, 1, and 6 months in alcoholic patients without cirrhosis. Seroconversion was found in 75% of patients receiving the high dose compared to 46% in the standard dose (*P* < 0.005). However, less than 10% of the patients in this study had cirrhosis (88). Horlander et al. studied 140 patients with cirrhosis over a 4-year period. Patients received 40 µg of recombinant vaccine at 0, 1, and 4 months. The seroconversion rate was only 37% at 3 months after vaccination. Furthermore, 35% of responders lost detectable hepatitis B antibody after liver transplantation (54). A similar response was found in a recent study from Spain, where a 40-µg dose given at 0, 1, and 2 months yielded a 44% seroconversion rate in patients with end-stage liver disease awaiting transplantation (30). Repeated vaccination cycle in the 28 nonresponders increased the rate of seroconversion to 62%. Others have confirmed the loss of titers after transplantation (8, 74). Factors that are associated with better response to the hepatitis B vaccine include age (younger versus older) and low Child score (8). The role of underlying chronic hepatitis C is controversial (69, 101).

In chronic hemodialysis patients two different protocols, 5 µg subcutaneously every 2 weeks versus 40 µg intramuscularly at 0, 1, 2, and 6 months were compared. The response rate (peak antibody titer >1,000 IU/liter) was similar in both groups (97% versus 90%), and vaccination appeared effective in this patient population (23, 82).

Current recommended dose of recombinant hepatitis B vaccine in patients with end-stage liver and renal disease waiting transplantation is 40 µg in at least three repeated doses. The vaccine should be given as early as possible in the course of the disease to obtain the best response. Monitoring of titers can be useful in identifying those patients with antibodies levels lower

than 10 mIU/ml who are not protected against the infection. Additional booster doses and revaccination at intervals of 2 to 3 years has been proposed (52). However, the validity of such measures needs to be confirmed by controlled studies, and the protocol indicated in this article reflects the personal views of the authors.

Diphtheria and Tetanus

The few data available on the efficacy of diphtheria and tetanus vaccinations in solid-organ recipients come from the pediatric population (12). In our opinion a vaccination campaign for diphtheria and tetanus is also of interest for an adult population, where it can result in improvement in immunity with minimal side effects (24).

Patients with cirrhosis produce a good antibody response to a booster dose of diphtheria and tetanus toxoid (12). Instead, in a study of 164 renal transplant recipients, investigators found that the prebooster levels of antibodies for tetanus and diphtheria antitoxin were lower than in healthy controls (55). The immunity after primary immunization for tetanus and diphtheria was also lower in 54 pediatric kidney recipients compared to normals (41). Renal recipients responded well to the booster dose of tetanus and inactivated polio vaccine but poorly to diphtheria (55). Booster vaccination for both diphtheria and tetanus was effective and safe in pediatric renal transplant recipients who had received their primary immunization before transplant (34). However, titers to diphtheria declined rapidly in the first 12 months after transplant, confirming what has been found in younger patients (81). This led to the recommendation in patients after renal transplantation to routinely administer tetanus and diphtheria boosters at regular intervals and assess postvaccination titers every 5 years for tetanus and not later than 2 years after vaccination for diphtheria. Whether these recommendations apply for adult recipients of other organs is not known, in particular considering the rarity of diphtheria in the United States

Other Vaccines

Tick-borne encephalitis is endemic in areas of central and eastern Europe. Caused by an RNA flavivirus, there were approximately 350 cases registered in Germany in 1997 (87). Vaccination for tick-borne encephalitis has been studied in heart transplant recipients, who have a significant depressed response compared to controls, with seroconversion rates of 35% versus 100% of controls (29).

Haemophilus influenzae type b may cause severe pneumonia after solid-organ transplantation, and vaccination with the bacterial capsular polysaccharide vaccine has been recommended in pediatric patients (20, 82). A recent study from Turkey, in adult renal recipients, showed the vaccine to be safe and effective (91). *H. influenzae* type b vaccination is also known to be safe and effective in bone marrow recipients and patients with human immunodeficiency virus (82). For these reasons, vaccination for *H. influenzae* type b has been recommended in solid-organ recipients who are not immune to the infection. We should mention, however, that most adults have protective antibody titer to *H. influenzae* type b and many *H. influenzae* type b infections are from nontypeable strains and therefore not protected by the vac-

cine. Whether pretransplant screening for protective antibodies is warranted has not been determined.

The quadrivalent polysaccharide vaccine for *Neisseria meningitidis* has been recommended in specific groups at higher risk of infection, including college-age patients, travelers to endemic areas and areas with active outbreaks, military recruits, patients with functional and anatomical asplenia, and those with deficiencies of the terminal components of complement. No information is available on solid-organ transplant recipients. We agree that the vaccine should be offered to those of college age and any other recipients who fall under the above categories (20).

Recent concerns for bioterrorism raised interest for a widespread vaccination campaign for vaccinia viruses. A vaccination campaign for the general population is under debate while vaccination programs for healthcare workers and military personnel have started in the United States. Smallpox vaccine, a live attenuated vaccine, has been associated with fatal disease in immunocompromised hosts. Furthermore, big concerns exist for possible secondary infection of immunosuppressed individuals from family members and health care workers who received the vaccine (90). For these reasons vaccinia vaccine is contraindicated in solid-organ transplant recipients, their family members, and health care providers working in transplant centers (90). The possible impact of a widespread vaccination campaign with the current available vaccine preparation on patients after solid-organ transplantation is unknown but worrisome.

Rabies is a rare but fatal disease in humans, with mortality close to 100% in infected patients even if they are immunocompetent. Transmission of rabies by corneal transplantation has been described (53). Pre- and postexposure prophylaxis remains the only effective therapy. Rabies vaccine is a human diploid cell inactivated vaccine that is used both before and after exposure to infected animals. From four to eight doses of vaccine given by the intradermal route, combined with passive prophylaxis with immunoglobulins, is the recommended therapy in exposed individuals (56). No studies are available to address vaccine efficacy and safety in solid-organ transplant recipients. Avoidance of occupations potentially at risk is recommended as well as aggressive therapy after exposure in these patients.

CONCLUSIONS

Despite emerging evidence that vaccinations are safe and effective among immunosuppressed patients, most vaccines are still underutilized in these patients (49). The following general principles apply to immunizations in transplant recipients. (i) The efficacy of the vaccination, as measured by antibody response, is usually decreased compared to normal subjects. (ii) Effective protection from the vaccination can be lost at an earlier time. (iii) Safety profiles are modified and specific complications such as rejection and graft dysfunction exist, at least theoretically. (iv) Live attenuated vaccines are usually contraindicated. (v) Immune response is best when the vaccine is administered prior to the start of immunosuppression.

We conclude that solid-organ recipients will benefit from consistent immunization practices. Most vaccinations with inactivated and killed microorganisms appear safe in solid-organ transplant recipients, and the side effects are minimal and

self-limited. Further studies are recommended to improve established protocols in this patient population, since most of the studies have enrolled a limited number of patients.

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